(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number
WO 2004/052374 A1

(51) International Patent Classification[7]: A61K 31/575, A61P 11/00, A61K 9/00

(21) International Application Number:
PCT/EP2003/014045

(22) International Filing Date:
11 December 2003 (11.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02027797.6 12 December 2002 (12.12.2002) EP
103 06 213.0 13 February 2003 (13.02.2003) DE

(71) Applicant *(for all designated States except US)*: **ALTANA PHARMA AG** [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DIETZEL, Klaus** [DE/DE]; Thingoltstr. 2e, 78465 Konstanz (DE). **MARX, Degenhard** [DE/DE]; Obere Reute 15, 78345 Moos (DE). **MÜLLER, Helgert** [DE/DE]; Zum Lerchental 1a, 78315 Radolfzell (DE). **WEIMAR, Christian** [DE/DE]; Eichhornstr. 51, 78464 Konstanz (DE).

(74) Agent: **KRATZER, BERND**; c/o ALTANA Pharma AG, Byk-Gulden-Str.2, 78467 Konstanz (DE).

(81) Designated States *(national)*: AE, AL, AU, BA, BR, CA, CN, CO, DZ, EC, EG, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, US, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

**Declarations under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AL, AU, BA, BR, CA, CN, CO, DZ, EC, EG, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, VN, YU, ZA, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)*
— *of inventorship (Rule 4.17(iv)) for US only*

**Published:**
— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: COMBINATION MEDICAMENT

(57) Abstract: The invention relates to the combination of ciclesonide with R,R-formoterol.

WO 2004/052374 A1

**Combination medicament**

## Field of application of the invention

The invention relates to a novel combination preparation for the therapy of airway diseases.

## Known technical background

Various novel glucocorticoids are disclosed, inter alia also the active compound ciclesonide, in DE-A 41 29 535. The combination of selected glucocorticoids with specific $\beta_2$-sympathomimetics is described in various patent applications (e.g. EP 0 416 950, EP 0 416 951, WO93/11773 or DE-A 19541689). WO01/89492 relates to a stable powder formulation comprising formoterol, a glucocorticosteroid and a carrier or diluent for use in the treatment of respiratory diseases.

## Description of the invention

It was the object of the present invention to make available an antiasthmatic to be administered locally, which fulfils the following conditions:

- good local (topical) action
- lack of systemic (side) effects
- low oral bioavailability
- rapid resolution of bronchospasm
- good antiinflammatory action
- good suitability for long-term therapy
- favourable influence on bronchial hyperreactivity.

It has now been found that the combined use of the active compound ciclesonide with the $\beta_2$-sympathomimetic R,R-formoterol fulfils the abovementioned conditions in an outstanding manner.

The invention thus relates to the combined use of ciclesonide with R,R-formoterol in the treatment of airway diseases.

Ciclesonide is the INN for an active compound having the chemical name [11β,16α-(R)]-16,17-[(cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-diene-3,20-dione. Cicle-

sonide and its preparation are described in DE-A 4129535. According to the invention, the name ciclesonide also includes solvates of ciclesonide, physiologically functional derivatives of ciclesonide or solvates thereof. Physiologically functional derivatives of ciclesonide, which can be mentioned in connection with the present invention, are preferably chemical derivatives of ciclesonide which have a similar physiological function to ciclesonide, for example the 21-hydroxy derivative of ciclesonide. The 21-hydroxy compound has the chemical name 16α,17-(22R,S)-cyclohexylmethylenedioxy-11β,21-dihydroxy-pregna-1,4-diene-3,20-dione. This compound and its preparation are disclosed in WO 94/22899. According to the invention, the name "ciclesonide" is understood as meaning not only the pure R epimer of the compound [11β,16α]16,17-[(cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-di-ene-3,20-dione but also R/S epimer mixtures in any desired mixing ratio (that is the compounds [11β,16α(R)]16,17-[(cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-diene-3,20-dione and [11β,16α(S)]-16,17-[(cyclohexylmethylene)bis(oxy)]-11-hydroxy-21- (2-methyl1-oxopropoxy)pregna-1,4-diene-3,20-dione), those being preferred which essentially consist of R epimers. According to the invention, essentially consisting of R epimers means that the proportion of S epimers in the mixture is less than or equal to 5%, preferably less than or equal to 1%.

Formoterol is the chemical compound N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)phenyl]formamide. Formoterol can exist in the form of various stereoisomers. The combinations according to the invention are preferably the combination of ciclesonide with R,R-formoterol. According to the invention, the active compound name R,R-formoterol can also include mixtures of various stereoisomers of formoterol. Preferably, such mixtures essentially consist of R,R-formoterol. According to the invention, consisting essentially of R,R-formoterol means that the proportion of R,R-formoterol in the mixture of the stereoisomers of formoterol is greater than or equal to 95%, preferably greater than or equal to 99%. Stereoisomers of formoterol are described, for example, in WO98/21175, WO99/17754, US 6068833 and US 5795564. US 6268533, US 6472563 and WO 00/21487 are related to a specific salt of R,R-Formoterol, the L-tartrate salt of formoterol. WO01/89491 is related to a novel micronisation process for manufacturing a stable formulation for formoterol and a carrier/diluent comprising a carbohydrate such as a lactose. WO98/31351 is related to a dry powder composition comprising formoterol and a carrier substance, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml. WO01/39745 is related to a dry powder composition comprising formoterol and a pharmaceutically acceptable particulate diluent or carrier in an amount of 400µg to 5000µg per µg of formoterol.

R,R-Formoterol can be present as such or in chemically bonded form. It is understood by this that R,R-formoterol can also be present in the form of pharmacologically tolerable salts and/or as solvates (e.g. hydrates) etc. Suitable pharmacologically tolerable salts here are in particular water-soluble and water-insoluble acid addition salts with acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)

benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic, methanesulphonic acid, or 1-hydroxy-2-naphthoic acid, it being possible for the acids to be employed in the salt preparation - depending on whether it is a mono- or polybasic acid and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom. In an embodiment of the invention R,R-formoterol is present in the medicament according to the invention as salt with an acid selected from the group of hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl) benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic, methanesulphonic acid and 1-hydroxy-2-naphthoic acid.

Preferably, the fumarate of R,R-formoterol may be mentioned, particularly preferably in the form of the dihydrate.

Airway diseases which may be mentioned are in particular allergen- and inflammatorily-induced bronchial diseases [bronchitis, obstructive bronchitis (in particular COPD = chronic obstructive pulmonary disease), spastic bronchitis, allergic bronchitis, allergic asthma, bronchial asthma], which can be treated by the combination according to the invention also in the sense of a long-term therapy (if desired with respective adjustment of the dose of the individual components to the present conditions, for example the conditions subject to variations related to the time of year).

Within the meaning of the present invention, "use" is primarily understood as meaning topical application in inhalative form. For this, the active compounds are preferably administered inhalatively in the form of aerosols, the aerosol particles preferably having a diameter of 0.5 to 10 µm, advantageously of 2 to 6 µm. The aerosol can be generated in the manner known to the person skilled in the art, e.g. by propellant-free use of micronized active compounds from inhalation capsules.

Combined use within the meaning of the present invention can be understood as meaning that the substances are simultaneously administered inhalatively from an apparatus suitable for this. Preferred apparatuses, which may be mentioned here are powder inhalers (dry aerosol generators). In this context, the substances can be present already mixed, or they can be taken out simultaneously from separate pack units during inhalation.

The use of two separate pack units offers the advantage that the dose of ciclesonide to be administered on the one hand and of R,R-formoterol on the other hand can be matched with one another and can be exactly suited to the individual case.

Combined use is in the sense of the present invention, however, can also be understood as meaning that the administration of the individual components takes place directly one after the other or else also

with a relatively large time interval, advantageously the R,R-formoterol first being administered inhalatively in order to relax the airways for the subsequent administration of the ciclesonide in order to ensure a higher and more uniform deposition of the ciclesonide in the airways and in the lung.

According to the invention, combined use or combination in particular also means that the active compounds ciclesonide and R,R-formoterol act in a synergistic manner (i.e. superadditive manner).

The active compounds are administered in an order of magnitude customary for the individual dose, it being possible on account of the mutually positively influencing and reinforcing individual actions to lower the respective doses in the combined administration of the active compounds compared with the norm. Customarily, the ciclesonide is administered, if desired in the form of a single, double or triple dose per day, in a dose of 0.05 to 1 mg per day. The R,R-formoterol is administered in a dose of 10 to 50 µg per day by means of a single, double or triple dose per day.

The present invention is further related to a method of treatment of an airway disease in a patient comprising administration of a therapeutically effective amount of a medicament according to the present invention to the patient in need thereof by means of a dry powder inhaler. Preferably the airway disease is a allergen- and inflammatorily-induced bronchial disease such as bronchitis, obstructive bronchitis, COPD (chronic obstructive pulmonary disease), spastic bronchitis, allergic bronchitis, allergic asthma and bronchial asthma.

In a preferred embodiment ciclesonide is administered in a dose of 0.05 to 1 mg per day and R,R-formoterol is administered in a dose of 10 to 50 µg per day in the method of treatment according to the present invention. In a particularly preferred embodiment the method of treatment according to the present invention is a once daily administration regimen.

In addition to the active compounds, the administration forms according to the invention if desired additionally contain the excipients and or vehicles necessary or optionally further active compounds. According to the invention, these are those excipients and or vehicles which are needed for administration forms which are administered by means of powder inhalers. By way of example, fillers such as, for example, lactose in powder inhalers may be mentioned here.

For the purposes of inhalation, in the case of powder inhalers a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler systems described in European patent applications EP 0 505 321, EP 407028, EP 650410, EP 691865 or EP 725725), using which an optimum administration of active compound is achievable.

**Example**

**Inhalation capsule**

In a Turbula mixer, 400 mg of micronized ciclesonide, 119 mg of micronized formoterol fumarate dihydrate (= 93 mg formoterol) and 36.1 g of lactose monohydrate Ph. Eur. II are mixed in two portions. The mixture screened through a 0.71 mm screen is transferred to the mixing container of a planetary mixer. After admixing a further 63.0 g of lactose monohydrate Ph. Eur. II, 25 mg of the powder mixture are filled into capsules of size 3, which can be administered using a commercially available powder inhaler. One puff of spray contains 100 µg of ciclesonide and 24 µg of R,R-formoterol.

**Multidose powder inhaler**

1000 g of lactose monohydrate (Ph. Eur. 4) are added through a screen mill. In a Turbula mixer, 300 mg of micronized R,R-formoterol fumarate dihydrate, screened through a 0.5 mm screen, and 97.2 g of the deagglomerated lactose monohydrate are mixed. 250 g of the deagglomerated lactose monohydrate are filled into a stirrer/mixer and mixed with 2.5 g of ciclesonide micronized screened through a 0.5 mm screen. The formoterol-lactose premixture is added through a 0.5mm screen to the mixing container of the stirrer/mixer and briefly intermixed. After admixing a further 650 g of deagglomerated lactose monohydrate, 1.5 g of the powder mixture are filled into the powder reservoir of a multidose powder inhaler using a suitable filling machine. After closing the reservoir chamber with a stopper, the attachment of the mouthpiece and/or the protective cap, the powder inhaler is sealed into a suitable protective film for protection from atmospheric moisture. A powder inhaler contains at least 60 individual doses (20.0 mg of powder) for each 50 µg of ciclesonide and 6 µg of R,R-formoterol fumarate dihydrate.

Multidose powder inhaler

60 mg of micronized formoterol fumarate dihydrate and 7.27 g of lactose monohydrate Ph. Eur. 4 are screened through a 0.5mm screen and mixed in the Turbula mixer. The formoterol-lactose premixture is again screened through a 0.5mm screen and added with 2.67 g of the screened micronized ciclesonide and 90 g of screened lactose monohydrate Ph. Eur. 4 to a stainless steel vessel and mixed in the Turbula mixer. 1.2 g of the powder mixture are filled into the powder reservoir of a multidose powder inhaler using a suitable filling machine. After closing the reservoir chamber with a stopper, the attachment of the mouthpiece and/or the protective cap, the powder inhaler is sealed into a suitable protective film for protection from atmospheric moisture.

A powder inhaler contains at least 120 individual doses (7.5 mg of powder) for each 200 µg of ciclesonide and 4.5 µg of R,R-formoterol fumarate dihydrate.

**Patent Claims**

1. Medicament containing the active compound ciclesonide and R,R-formoterol in a fixed or free combination.

2. Medicament for the treatment of airway diseases, containing the active compound ciclesonide and R,R-formoterol in fixed or free combination and together with customary excipients or vehicles in an administration form suitable for inhalative administration by means of a powder inhaler.

3. Medicament according to Claim 2, characterized in that the active compound ciclesonide and R,R-formoterol are present ready mixed in a fixed combination .

4. Medicament according to Claim 3, characterized in that lactose is present as an excipient or vehicle.

5. Medicament according to Claim 2, characterized in that the active compound ciclesonide and the R,R-formoterol are present in separate pack units, it being possible to take out the active compound ciclesonide and the R,R-formoterol from the separate pack units such that they are available for simultaneous inhalative administration.

5. Medicament according to Claim 2, characterized in that the active compound ciclesonide and the R,R-formoterol are present in separate pack units, the active compound ciclesonide and the R,R-formoterol being taken out of the separate pack units such that they are administered successively inhalatively.

6. Medicament according to Claim 2, characterized in that the active compound ciclesonide is present to more than 95 % in the form of its R epimer.

7. Medicament according to Claim 2 or 3, characterized in that the active compound ciclesonide is present to more than 95 % in the form of its R epimer and the active compound R,R-formoterol is a salt and/or hydrate of this active compound.

8. Medicament according to Claim 7, characterized in that R,R-formoterol is present as salt with an acid selected from the group of hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl) benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid,

succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic, methanesulphonic acid and 1-hydroxy-2-naphthoic acid.

9. Medicament according to claim 8, wherein the acid is fumaric acid or tartaric acid.

10. Use of the active compound ciclesonide in fixed or free combination with R,R-formoterol in the treatment of airway diseases .

11. Use according to Claim 10, where the combination is a fixed combination and the active compounds are present in a form suitable for inhalative administration by means of a powder inhaler.

12. Use according to Claim 10, characterized in that the active compound ciclesonide is present to more than 95 % in the form of its R epimer.

13. Method of treatment of an airway disease in a patient comprising administration of a therapeutically effective amount of a medicament according to claim 2 or 3 to the patient in need thereof by means of a dry powder inhaler.

14. Method according to claim 13, wherein the airway disease is a allergen- and inflammatorily-induced bronchial disease such as bronchitis, obstructive bronchitis, COPD (chronic obstructive pulmonary disease), spastic bronchitis, allergic bronchitis, allergic asthma and bronchial asthma.

15. Method according to claim 13, wherein ciclesonide is administered in a dose of 0.05 to 1 mg per day and R,R-formoterol is administered in a dose of 10 to 50 µg per day.

16. Method according to claim 15, which is a once daily administration regimen.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14045

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/575 A61P11/00 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 03 086349 A (JINKS PHILIP A ;OLIVER MARTIN J (GB); 3M INNOVATIVE PROPERTIES CO) 23 October 2003 (2003-10-23) claims 1-15; examples 1,2 --- | 1,10 |
| P,X | US 6 536 427 B2 (DAVIES MICHAEL BIRSHA ET AL) 25 March 2003 (2003-03-25) claims 1-23 --- | 1,10 |
| X | DE 195 41 689 A (BYK GULDEN LOMBERG CHEM FAB) 15 May 1996 (1996-05-15) cited in the application claims 1-10 --- | 1-16 |
| X | WO 02 062317 A (INNOVATA BIOMED LTD ;SANDERS MARK (GB)) 15 August 2002 (2002-08-15) claims 1-54 --- | 1-16 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 18 March 2004 | 24/03/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Stienon, P |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14045

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02 083113 A (BANERJEE PARTHA S ;CHAUDRY IMITIAZ A (US); DEY L P (US)) 24 October 2002 (2002-10-24) claims 1,31,51 page 4, line 2 - line 7 page 17, line 5 - line 12 page 23, line 1 --- | 1-16 |
| X | WO 00 28979 A (SKYEPHARMA AG ;MUELLER WALZ RUDI (DE); KELLER MANFRED (DE)) 25 May 2000 (2000-05-25) claims 1,15,17,21,22,30 --- | 1-16 |
| X | WO 00 07567 A (HERZOG KURT ;JAGO RES AG (CH); KRAUS HOLGER (CH); MUELLER WALZ RUD) 17 February 2000 (2000-02-17) claims 1-18 ----- | 1-16 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/14045

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 13-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

---

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/14045

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 03086349 A | 23-10-2003 | WO 03086349 A1 | 23-10-2003 |
| US 6536427 B2 | 09-05-2002 | US 6378519 B1 | 30-04-2002 |
| | | US 6032666 A | 07-03-2000 |
| | | US 5860419 A | 19-01-1999 |
| | | US 5873360 A | 23-02-1999 |
| | | US 5590645 A | 07-01-1997 |
| | | US 2002053344 A1 | 09-05-2002 |
| | | AP 310 A | 07-01-1994 |
| | | AT 401007 B | 28-05-1996 |
| | | AT 43791 A | 15-10-1995 |
| | | AU 675825 B2 | 20-02-1997 |
| | | AU 5926794 A | 16-06-1994 |
| | | AU 645056 B2 | 06-01-1994 |
| | | AU 7202591 A | 05-09-1991 |
| | | BE 1003798 A4 | 16-06-1992 |
| | | BR 9100843 A | 05-11-1991 |
| | | CA 2037421 A1 | 03-09-1991 |
| | | CA 2288413 A1 | 03-09-1991 |
| | | CH 683319 A5 | 28-02-1994 |
| | | CN 1054893 A ,B | 02-10-1991 |
| | | CN 1107687 A ,B | 06-09-1995 |
| | | CZ 283168 B6 | 14-01-1998 |
| | | CZ 9601807 A3 | 16-12-1998 |
| | | CY 2010 A | 20-02-1998 |
| | | CY 2014 A | 20-02-1998 |
| | | CZ 285501 B6 | 11-08-1999 |
| | | DE 4106379 A1 | 05-09-1991 |
| | | DK 37991 A | 03-09-1991 |
| | | ES 2031763 A6 | 16-12-1992 |
| | | FI 911037 A | 03-09-1991 |
| | | FI 990115 A | 21-01-1999 |
| | | FR 2659558 A1 | 20-09-1991 |
| | | FR 2660550 A1 | 11-10-1991 |
| | | GB 2242134 A ,B | 25-09-1991 |
| | | GB 2274273 A ,B | 20-07-1994 |
| | | GR 91100096 A ,B | 30-06-1992 |
| | | HK 18895 A | 17-02-1995 |
| | | HK 19195 A | 17-02-1995 |
| | | HR 940631 A1 | 31-08-1996 |
| | | ID 20246 A | 05-11-1998 |
| | | IE 910698 A1 | 11-09-1991 |
| | | IL 97396 A | 31-12-1995 |
| | | IT 1244655 B | 08-08-1994 |
| | | JP 3110477 B2 | 20-11-2000 |
| | | JP 4220266 A | 11-08-1992 |
| | | KR 210412 B1 | 15-07-1999 |
| | | KR 244004 B1 | 15-03-2000 |
| | | LU 87898 A1 | 16-11-1992 |
| | | NL 9100381 A ,B, | 01-10-1991 |
| | | NO 910836 A | 03-09-1991 |
| | | NO 302929 B1 | 11-05-1998 |
| DE 19541689 A | 15-05-1996 | DE 19541689 A1 | 15-05-1996 |
| WO 02062317 A | 15-08-2002 | CA 2435982 A1 | 15-08-2002 |
| | | EP 1359902 A2 | 12-11-2003 |
| | | WO 02062317 A2 | 15-08-2002 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/14045

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 02062317 A | | NO 20033451 A | 03-10-2003 |
| WO 02083113 A | 24-10-2002 | US 2003055026 A1 | 20-03-2003 |
| | | CA 2444535 A1 | 24-10-2002 |
| | | EP 1385494 A2 | 04-02-2004 |
| | | WO 02083113 A2 | 24-10-2002 |
| | | US 2002183293 A1 | 05-12-2002 |
| WO 0028979 A | 25-05-2000 | AT 233550 T | 15-03-2003 |
| | | AU 756852 B2 | 23-01-2003 |
| | | AU 6457899 A | 05-06-2000 |
| | | CA 2347856 A1 | 25-05-2000 |
| | | WO 0028979 A1 | 25-05-2000 |
| | | CN 1326341 T | 12-12-2001 |
| | | CZ 20011553 A3 | 12-09-2001 |
| | | DE 59904488 D1 | 10-04-2003 |
| | | DK 1131059 T3 | 30-06-2003 |
| | | EP 1283036 A1 | 12-02-2003 |
| | | EP 1131059 A1 | 12-09-2001 |
| | | ES 2192866 T3 | 16-10-2003 |
| | | HU 0104226 A2 | 28-02-2002 |
| | | JP 2002529498 T | 10-09-2002 |
| | | NO 20012346 A | 26-06-2001 |
| | | NZ 511527 A | 25-10-2002 |
| | | PL 347640 A1 | 22-04-2002 |
| | | PT 1131059 T | 31-07-2003 |
| | | SK 6322001 A3 | 07-01-2002 |
| | | US 6645466 B1 | 11-11-2003 |
| | | ZA 200103627 A | 09-05-2001 |
| WO 0007567 A | 17-02-2000 | AT 234604 T | 15-04-2003 |
| | | AU 749697 B2 | 04-07-2002 |
| | | AU 4893999 A | 28-02-2000 |
| | | CA 2338680 A1 | 17-02-2000 |
| | | WO 0007567 A1 | 17-02-2000 |
| | | CN 1315852 T | 03-10-2001 |
| | | DE 59904648 D1 | 24-04-2003 |
| | | DK 1102579 T3 | 14-07-2003 |
| | | EP 1102579 A1 | 30-05-2001 |
| | | ES 2193726 T3 | 01-11-2003 |
| | | JP 2002522374 T | 23-07-2002 |
| | | NO 20010531 A | 31-01-2001 |
| | | NZ 509489 A | 25-10-2002 |
| | | PT 1102579 T | 31-07-2003 |
| | | US 6475467 B1 | 05-11-2002 |
| | | ZA 200100569 A | 30-07-2001 |